Review

Review of the Effect of Natural Compounds and Extracts on Neurodegeneration in Animal Models of Diabetes Mellitus

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Abstract: Diabetes mellitus is a chronic metabolic disease with a high prevalence in the Western population. It is characterized by pancreas failure to produce insulin, which involves high blood glucose levels. The two main forms of diabetes are type 1 and type 2 diabetes, which correspond with >85% of the cases. Diabetes shows several associated alterations including vascular dysfunction, neuropathies as well as central complications. Brain alterations in diabetes are widely studied; however, the mechanisms implicated have not been completely elucidated. Diabetic brain shows a wide profile of micro and macrostructural changes, such as neurovascular deterioration or neuroinflammation leading to neurodegeneration and progressive cognition dysfunction. Natural compounds (single isolated compounds and/or natural extracts) have been widely assessed in metabolic disorders and many of them have also shown antioxidant, antiinflamatory and neuroprotective properties at central level. This work reviews natural compounds with brain neuroprotective activities, taking into account several therapeutic targets: Inflammation and oxidative stress, vascular damage, neuronal loss or cognitive impairment. Altogether, a wide range of natural extracts and compounds contribute to limit neurodegeneration and cognitive dysfunction under diabetic state. Therefore, they could broaden therapeutic alternatives to reduce or slow down complications associated with diabetes at central level.

Keywords: type 2 diabetes; inflammation; vascular damage; learning; memory; neuroprotection; natural extract; natural compound

1. Type 2 Diabetes Mellitus: Central Complications

Metabolic disorders include a broad range of alterations. Moreover, the terminology used to refer to many of the diseases and complications is confusing in many cases [1,2]. Among these, diabetes mellitus (DM) plays a preponderant role, due to its prevalence and societal and economical burden. In 2013 over 380 million people suffered diabetes and it is estimated that by 2035 there will be 592 million diabetic patients [3]. World Health Organization (WHO) defines DM as a chronic metabolic disease caused by inherited and/or acquired deficiency in the production of insulin by the pancreas, or by the ineffectiveness of the insulin produced. Such a deficiency results in increased concentrations of glucose in the blood, which in turn damage many of the body's systems, in particular the blood vessels and nerves [4]. The two main forms of diabetes are type 1 diabetes (T1D) and type 2 diabetes (T2D), which account for >85% of the cases [3]. T1D and T2D differentially impact populations based on age, race, ethnicity, geography and socioeconomic status [5]. T1D is the most frequent type of diabetes in children and adolescents [6]. T1D patients suffer the destruction of over

90% of β-pancreatic islets, with consequent reduction of insulin and glycaemia control. On the other hand, T2D affects adults preferentially. However, the prevalence of T2D in adolescents and young adults is dramatically increasing [7]. T2D is characterized by an initial stage of insulin resistance. To compensate hyperglycaemia, β-pancreatic cells respond by increasing insulin production and establishing a prediabetic state. When exhausted β-pancreatic cells can no longer overproduce insulin, diabetes evolves. T2D is associated to a large list of risk factors, including familiar risk, previous gestational diabetes or life styles, among others [8].

While peripheral micro and macrovascular complications associated with T2D, such as neuropathies, retinopathies or nephropathies, have been widely studied [9], only in recent years attention has been paid to central complications associated with long-term metabolic alterations [10]. The mechanisms implicated have not been completely elucidated; however, cognitive impairment, vascular dementia, Alzheimer's disease, stroke or anxiety/depression have been related to diabetes [1,11]. In this sense, the diabetic brain (with controlled or uncontrolled hyperglycemia) show brain injury with a wide profile of micro and macrostructural changes, leading to neurodegeneration, neurovascular deterioration, neuroinflammation and progressive cognition dysfunction [12–19]. However, the study of central complications associated with T2D has been probably hampered by the difficulty of the measurements [2], the lack of ideal animal models, or the fact that T2D is a complex disorder and, therefore, it is likely that multiple different, synergistic processes may interact to promote central alterations. Accordingly, the vast majority of the research are epidemiological studies in which T2D is identified as a risk factor for Alzheimer's disease or vascular dementia [20–23]. Only a few studies have captured quality data regarding metabolic and cognitive status to allow reliable diagnosis of both T2D and dementia subtype. Main limitations are due to the fact that many of the studies rely on self reported diabetes, underestimating the prevalence by up to 50%, medical records are incomplete or may even include undiagnosed diabetics as control samples [2]. Moreover, patients with diabetes are often presumed to have dementia of vascular origin. However, the main limitation might be to determine the effects of medication, since treatments for T2D may also affect brain-associated complications [2]. Hence, in order to accurately delineate the pathogenesis of cognitive impairment in people with T2D, large-scale, prospective epidemiological studies are still required [24].

2. Natural Compounds and Central Complications in DM

The wide and countless number of natural compounds from plants, animals, fungi, microorganisms and other natural resources provides a rich and a unique source in the search of new drugs [25]. The potential health risk in the indiscriminate use of natural products cannot be obviated [26]. However, plant compounds, including different natural products (single isolated compounds) and/or natural extracts (including different compounds and/or secondary metabolites), have been long analyzed and assessed in relation with different pathologies. Usually, biological activity in plants' natural extracts is mainly due to secondary metabolites. Plant secondary metabolites include two extensive categories: Nitrogen-containing compounds and those without it [27,28]. In line with these observations, several studies have shown a wide range of biological activities in these extracts, including anti-inflammatory [29,30], anti-microbial [31], anti-diabetic [18,32] or neuroprotective [27,33,34] properties, among others.

One of the most extensive group of secondary metabolites in the plant kingdom are polyphenols [35]. Structurally, they are characterized by the presence of at least one hydroxyl functional group (-HO) linked to an aromatic ring [36]. Polyphenols classification is referred to the number of phenol rings in the molecule, and the main subgroups include phenolic acids, stilbenes, flavonoids, coumarins and lignans [35]. The wider group of polyphenols in plants is represented by flavonoids, which account for over 10,000 different compounds [28,35]. As other natural compounds, flavonoids have shown several properties including antioxidant, neuroprotective [37] or anti-diabetic [38–40] effect. Another particularity of polyphenols is their role in human nutrition, which extends their utility, including not

only a pharmacological, but also a nutritional perspective. This singularity of polyphenols contributes to further study of these compounds in other fields, such as human diet supplements [35,41].

As mentioned above, DM, or even prediabetes state, are associated with an increased risk to suffer neurodegenerative diseases, specially vascular dementia and Alzheimer's disease [42,43]. Therefore diabetic control may be an important and modifiable risk factor to reduce diabetes-associated neurodegeneration [44]. In this sense, while the number of articles published worldwide in relation with antidiabetic natural products is growing each year, most of them focus on metabolic control and related alterations [45]. On the other hand, studies on the effect of natural products and extracts on central complications associated with DM are more scarce. This is mainly due to the difficulty to identify individual components in complex extracts, the capability of different molecules to cross the blood brain barrier, or even discriminate the direct effect of diabetes on the pharmacokinetics, bioavailability and brain distribution of the compounds and metabolites [46]. However, given the well established complications of DM on the central nervous system, there are different targets of interest that may be covered by natural compounds, including vascular damage, neuroinflammation, neurodegeneration or cognition. Following this idea, several natural compounds and extracts have been reported to show neuroprotective effects [34,38].

2.1. Natural Compounds and DM-Related Vascular Injury

2.1.1. Vascular Damage and DM

Vascular complications are the leading cause of morbidity and mortality in diabetic patients. Vascular alterations are derived from the chronic hyperglycemic state that can affect both large and small blood vessels, characterizing diabetes macro and microangiopathy, respectively [47]. Several vascular alterations including irreversible non-enzymatic glycation of proteins, cellular redox potential alteration, increased oxidative stress or inflammatory response, as well as endothelial dysfunction or hypercoagulability contribute to vascular abnormalities associated to DM [47–49]. These underlying alterations may support the fact that diabetic patients present arterial stiffness as well as increased risk of atherosclerosis and cerebral stroke [50–52]. In line with these observations, previous studies have reported that DM patients have smaller brain volumes and white matter lesions, which have been associated to neurovascular unit dysfunction and blood brain barrier alterations. In this context T2D could cause loss of homeostasis of the cerebral microenvironment, leading to vascular damage and astrocyte alterations [53]. In addition, preclinical studies in diabetes animal models have shown exacerbated neurovascular damage, and ultrastructural abnormalities, characterized by mural endothelial cell tight and adherens junction or perycite attenuation or loss [54]. Likewise, studies in mouse models reveal brain overspread microbleeding, reproducing small vessel disease [55,56]. DM not only exacerbates neurovascular damage but also hinders the brain repair process, likely contributing to the impairment of stroke recovery [57]. In this sense, in vitro and in vivo experimental models have showed that the integrity of the blood brain barrier is affected in diabetic conditions [58–60]. Concretely, diabetes disrupts the blood brain barrier endothelium by downregulation of cell junction proteins [61–63] and upregulation of integrin expression [64,65], leading to abnormal vascular permeability [66,67]. In addition, this effect might be mediated by oxidative stress, which induces blood brain barrier disruption through osmotic damage and pericyte loss [68], ultimately leading to the leak of toxic substances and further damage to the nervous structures [69]. Interestingly, microvascular alterations seem to be present also in prediabetic animal models [70], suggesting that early hyperinsulinemia and insulin resistance are enough to induce vascular damage.

2.1.2. Natural Compounds and Extracts in Vascular Damage Associated with DM

In order to try and reverse many of these complications different natural compounds and extracts have been used in animal models. In this sense berberine, a protoberberine present in a number of medicinal plants [71], and the main active component of *Coptis chinensis French* has been used for

years, and studies in patients have shown its capability to regulate glucose and lipid metabolism [72]. Moreover, at central level it has also been reported that berberine may reduce diabetes induced ectopic expression of miR-133a in endothelial cells, which is involved in endothelial dysfunction in DM. In addition, berberine may inhibit acetylcholine-induced vasorelaxation in the middle cerebral artery, guaranteeing better blood supply to the brain in streptozotozin (STZ)-treated rats, as a T1D model [73]. It has also been reported that patchouli alcohol, a natural tricyclic sesquiterpene in the traditional Chinese herb Pogostemonisherba [74], reduces ishcemia/reperfusion damage after middle cerebral artery occlusion in ob/ob mice by limiting infarct volume, protecting blood brain barrier function and decreasing inflammatory markers [74]. In line with these observations, *Mangifera indica Lin* extract, rich in natural polyphenols, reduces spontaneous central bleeding detected in db/db mice. While the actual size of the microbleeds is not affected, *Mangifera indica* extract reduces the appearance of new vascular lesions [18]. In addition, poor cerebral perfusion may contribute to cognitive impairment in diabetic state and resveratrol, a natural phenol isolated from plants like *Polygonum cuspidatum*, *Paeonia lactiflora* and *Vitis amurensis*, among others [75], may improve neurovascular coupling capacity in T2D patients [76] and reduce blood brain barrier permeability and vascular endothelial growth factor expression in the hippocampus of diabetic rats [77] (Table 1 and Figure 1).
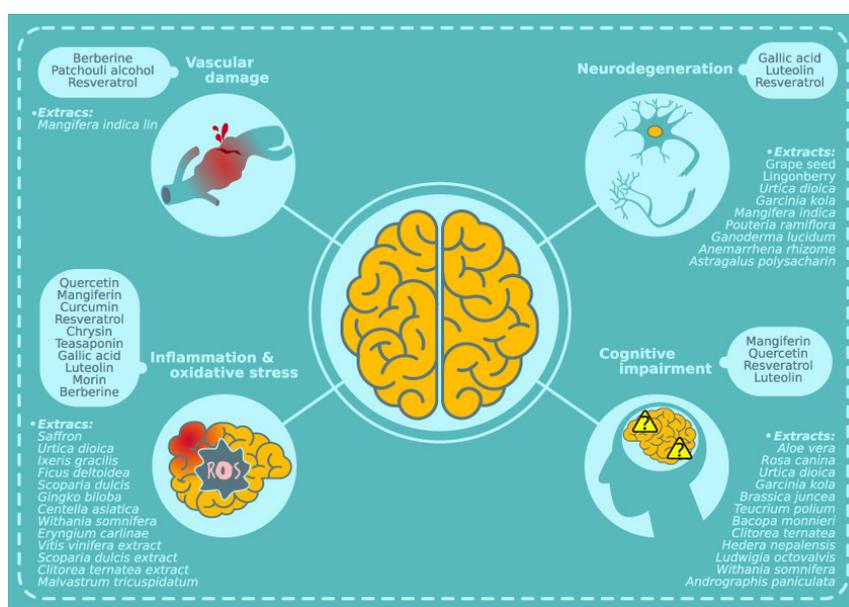

Figure 1. Central activities of natural compounds and extracts.

2.2. Natural Compounds and Neuroinflammation Associated with DM

2.2.1. Brain Neuroinflammation and DM

Inflammation is an immune response against several conditions including disease and infection. Acute inflammatory events are resolved efficiently and inflammation levels return to baseline in physiological conditions. However, in chronic inflammation the resolution phase is not achieved due to excessive pro-inflammatory signalling and it can provoke relevant detrimental effects [78]. Following this idea, insulin resistance and diabetes are closely associated with chronic inflammation [79]. Moreover, the finding two decades ago that proinflammatory cytokines like tumor necrosis factor-α (TNF-α), among others, are overexpressed in adipose tissue of obese mice provided a relation between obesity, diabetes and chronic inflammation [79–81].

Inflammation in the central nervous system is complexly regulated and astrocytes [82], blood inflammatory cells and even neurons seem to participate and mediate inflammation in the injured brain. However, microglia still play the most significant role at this level [83]. Microglia are a specific type of macrophage in the brain; they are held without external replenishment and they are not

in contact with plasmatic proteins, which contributes to keep an immupriviledged environment in the central nervous system [84]. The classical dual role of microglia as a protective (with a typical anti-inflammatory profile) or damaging agent (with a proinflammatory response) has been recently reviewed and microglia-mediated responses seem to be more prone towards neuronal survival, regeneration [85] and overall neuroprotection [86]. The role of microglia in neurodegenerative diseases has been long studied and they also seem to be highly activated in metabolic disease models, ranging from prediabetic [87], T1D [88], T2D [55,56] models, or even diabetic mothers offspring [89]. Under diabetic conditions, hyperglycemia leads to increased mitochondrial respiration in pericytes, astrocites as well as endothelial cells [90]. This causes an increase in the production of reactive oxygen species that may consequently lead to neurovascular damage and blood brain barrier dysfunction, contributing to the inflammatory process. Increased levels of reactive oxygen species may also affect protein fuction, signaling pathways or induce upregulation of inflammatory cytokines [90]. Therefore, previous studies have shown that, in metabolic alterations, microglia mediated neuroinflammation may contribute to the neurodegenerative process by promoting the release of cytokines and chemokines including TNF-α [91,92]. In line with these ideas, studies in patients with metabolic disorders have detected a decrease in mRNA levels of the IL10-mediated anti-inflammatory defense, while iNOS-mediated inflammatory activity seems to be favored in the cortex from obese patients [93].

2.2.2. Effect of Natural Compounds on DM-Related Inflammation

Antioxidant and anti-inflammatory activities are probably the most widely explored roles of natural compounds and extracts [30,94,95]. Following this idea, many studies have previously used products of natural origin to counterbalance oxidative stress, neuroinflammation and alterations in related markers and cytokines. Even though the role of flavonoids in neuroprotection might be due to different mechanisms of action it is mediated, at least in part, by direct scavenging of free radicals as antioxidant action [35,96]. Several plants extracts constitute a relevant source of polyphenols. While in many cases they share common mechanisms and show potent anti-inflammatory and antioxidant activities, not all of them have been completely characterized. Concretely quercetin, present in many fruits and vegetables, may enhance glyoxalase pathway activity, inhibit advanced glycation end products (AGEs) formation and reduce oxidative stress [97]. Quercetin is a flavonoid present in a wide variety of plants, including *Rosa canina*, *Opuntia ficusindica* and *Allium cepa* [75]. Oral administration of quercetin to diabetic rats has shown antioxidant effects, increasing superoxide dismutase (SOD) and catalase activity, while also restoring the blood levels of vitamin C and E, which finally contribute to ameliorate the diabetes-induced in oxidative stress [98]. On the other hand, it has been described that quercetin also protects neuronal PC12 cells against high-glucose-induced oxidative stress, inflammation and apoptosis [99]. While the final underlying mechanisms involved in quercetin neuroprotective effects are not completely known, a recent study has shown that neuroprotection might mediated by phosphorylation regulation of Nrf2/ARE/glyoxalase-1 pathway in central neurons under chronic hyperglycemia, reducing AGEs and oxidative stress [38]. In line with these observations mangiferin, which is mainly present in *Mangifera indica L.* but also in Chinese herbal medicines like *Rhizoma Anemarrhenae* and *Rhizoma Belamcandae*, has anti-inflammatory [100] and antioxidant [100,101] activities. Mangiferin also enhances the function of glyoxalase-1 through activation Nrf2/ARE pathway in neurons exposed to chronic high glucose [101]. In addition, *Mangifera indica L.* extracts with a high content in mangiferin and quercetin reduce microglia activation and associated inflammation in db/db mice after long-term treatment [18].

On the other hand curcumin, a bright yellow compound isolated from the rhizome of *Curcuma longa* [75] has shown neuroprotective effects in diabetic rats reducing blood glucose, oxidative stress markers and astrocyte activation in the hippocampus [102]. A recent study has reported the potent neuroprotective effect of J147, a novel curcumin derivative developed to increase curcumin bioavailability and blood brain barrier permeability [103]. J147 reduces inflammation by decreasing TNF-α pathway activation and several other markers of neuroinflammation in mice treated with STZ [103], supporting that

different curcumin extracts and derivates are potent antioxidants with the capability to limit associated central complications in diabetes. Resveratrol has a well established antioxidant activity. It reduces astrocytic activation as well as TNF-α, IL-6 transcripts the hippocampus of diabetic rats [77]. Resveratrol also normalizes malonedialdehyde and oxidezed glutathione levels in diabetic rats and it strengthens the action of antioxidants enzymes SOD and catalase [104]. *Ficus deltoidea* leaf extract also increases SOD and glutathione peroxidase values, while reducing thiobarbituric acid reactive substances [105]. Similar outcomes have been reported for saffron extracts with antidiabetic activity, which also modulate antiinflamatory pathways at central level [106]. Likewise, *Scoparia dulcis* plant extract also increases activities of plasma SOD, catalase or glutahione peroxidase or glutathione-S-transferase while reduces gluthatione in the brain from STZ diabetic male rats [107]. Similar outcomes have been described for chrysin, a flavonoid isolated from *Oroxylum indicum*, *Passiflora caerulea*, *Passiflora incarnata*, *Teloxys graveolens* and *Artocarpus heterophyllus* that also ameliorates oxidative stress by reducing catalase levels, SOD and glutathione in the cerebral cortex and hippocampus of diabetic rats [108].

One of the most widely studied preparations is Gingko biloba extract EGb 761, which has been described to scavenge reactive nitrogen and oxygen species, as well as peroxyl radicals [35,96,109]. A similar scavenging effect has been described for green tea extracts [35,110]. In this sense, tea extract, teasaponin, also reduces proinflammatory citokines and inflammatory signaling in the hypothalamus from mice on high fat diet [111]. For its part, *Clitorea ternatea* leaf extract, has showed protection against oxidative stress increasing SOD, total nitric oxide, catalase and glutathione levels in the brain of diabetic rats [112]. Similar antioxidant effects have been reported for grape seed extracts (*Vitis vinifera* sp.), rich in flavonoids like proanthocyanidins, showing beneficial effects on oxidative stress in the hippocampus of STZ-induced diabetes rats, to a larger extend than a classical antioxidant as viatamin E [113]. The expression of inflammatory TNF-α, and NF-κB genes are significantly reduced and other studies have also reported the role of grape seed extract in modulating AGEs/RAGE/NF-kappaB inflammatory pathway in the brain [114]. *Urtica dioica* leaves extract, rich in scopoletin, rutin, esculetin and quercetin, has also shown antioxidant and anti-inflamatory activities in the hippocampus from STZ-induced diabetic mice [115,116]. In addition, the number of astrocytes in the hippocampus from diabetic rats is reduced after treatment with *Urtica dioica* extract, supporting its anti-inflammatory role at different levels [117].

Gallic acid, is a type of phenolic acid, which is isolated from several plants including *Phaleria macrocarpa*, *Peltiphyllum peltatum*, and *Pistacia lentiscus*. Gallic acid may inhibit hippocampal neurodegeneration via its potent antioxidant and anti-inflammatory effects in diabetic rats [118]. Similarly, *Scoparia dulcis* extract also reduces thiobarbiyutic acid reactive substances and hydroperoxides formation in the brain from diabetic rats, supporting its role in protection against lipid peroxidation induced membrane damage [107]. Luteolin can also reduce neuroinflammation by reducing plasma and brain cytokines in a prediabetic mouse model [119]. Moreover, similar antioxidant and anti-inflammatory effects have been reported for luteolin in diabetic mice [120]. Other studies in prediabetic models have shown a protective role for *Withania somnifera*, which may reduce gliosis and microgliosis as well as expression of inflammation markers such as PPARγ, iNOS, MCP-1, TNF-α, IL-1β, and IL-6 [121]. In line with these observations, oral administration of an hexanic extract of *Eryngium carlinae* inflorescences to diabetic rats not only reduced glucose levels but also limited overall oxidation, by reducing lipid peroxidation, protein carbonylation and reactive oxigen species production, while increasing catalase activity in the brain [122]. Morin is another flavonoid isolated from *Maclura pomifera* and *Maclura tinctoria*, with similar properties [123,124]. Additionally, the flavonoid rutin has also shown antioxidant properties in the diabetic rat retina [125]. In line with these observations, berberine has been shown to reduce oxidative stress and astrogliosis in the hippocampus from diabetic rats [126]. A natural extract from *Centella asiatica,* rich in ascorbic acid, asiatic acid, oleanolic acid, stevioside, stigmasterol and α-humulene protects diabetes tissues from stress via antioxidant and anti-inflammatory mechanisms eliciting brain reduced levels of malondialdehyde, TNF-α, IFN-γ, IL-4 or IL10 [127]. Similar outcomes have been reported for *Ixeris gracilis* extract used in mice with alloxan-induced diabetes [128]. Specific assessment of mitochondrial status in

STZ-induced diabetes has also revealed the capacity of *Malvastrum tricuspidatum* extract to restore oxidative damage [129] (Tables 1 and 2, and Figure 1).

2.3. Natural Compounds and Brain Neurodegeneration in DM

2.3.1. Neurodegeneration in Diabetic Brain

A wide range of clinical [15,19,130,131] and preclinical studies [70,88,132] have shown an association of prediabetes and diabetes with brain atrophy. In this sense, magnetic resonance studies have shown that both T1D and T2D patients have reduced grey matter density and white matter lesions, as well as cortical and hippocampal atrophy [133,134]. However, it seems that brain atrophy is more severe in T2D patients, probably given that this population is older on average [135–137]. As previously pointed out, the prediabetes process seems to be enough to induce brain atrophy in patients [138] and synaptic loss is also detected in animal models when prediabetes is combined with other central complications [132]. Likewise, animal models of metabolic alterations show neuronal simplification, synaptic alterations [44], reduced neuronal density and overall brain atrophy [55,56].

Neurodegeneration in diabetes is mediated by multiple neuropathogenic factors including hyperglycemia mediated damage, but also hypoglycemic episodes, cerebrovascular alterations or insulin derregulation in the brain or among others [139]. In this sense, dysfunction of insulin/insulin receptor mediated signaling might be responsible for alterations in synaptic plasticity, cognition and memory [139,140]. Once more, oxidative stress mediated by free radicals is related with the diabetes neurodegenerative process [141], given that hyperglycemic state reduces antioxidants levels and consequently increases the production of free radicals [139]. Neurons are especially vulnerable to oxidative stress and this can induce mitochondrial oxidative damage, resulting in apoptosis and/or necrosis [142]. On the other hand, several proteins implicated in neurodegeneration, such as tau protein, which is hyperphosphorylated in diabetic mouse models, may also underlie neuronal death [70,88,143]. In overall terms, neurodegeneration is perceived as a cause of cognitive dysfunction observed in diabetes conditions.

2.3.2. Effect of Natural Compounds and Extracts on Brain Neurodegeneration Associated with DM

The majority of the studies on natural compounds and extracts have focused on their antioxidant and anti-inflammatory activities. However, neurodegeneration is a multifactorial pathogenic process and it is feasible than various, concomitant underlying mechanisms are responsible for their final neuroprotective effect. In this sense, polyphenols are able to modulate the activity of multiple involved targets, which contribute their pleiotropic effects (anti-inflamatory, antioxidant or inmunomodulatory) [144], and, indeed, phenolic compounds have shown their neuroprotective role in vitro, in animal models and in clinical studies [145–148]. In line with these observations, flavonoids are not only implicated in scavenging of free radicals and reducing oxidative stress [35,96], but they can also modulate brain signaling cascades implicated in neuronal apoptosis, alter the expression of specific genes and modify mitochondrial activity [149].

Mangifera indica extract has shown its capability to limit brain atrophy in db/db mice. Cortex and hippocampus are largely preserved after long-term administration [18]. Interestingly, oral treatment with *Mangifera indica* also reduces tau hyperphosphorylation, an early marker of neuronal damage, and it also preserves compromised neuronal population in this model [18]. In line with these observations quercetin has also been shown to protect neuronal PC12 cells against high-glucose-induced oxidative stress, inflammation and apoptosis [99], as described for gallic acid in diabetic mice [118]. Curcumin protects against structural alterations of the hippocampus associated with diabetes, by reducing disorganization of small pyramidal cells in CA1, cellular loss in the pyramidal cells of CA3 and degenerated granule cells in the dentate gyrus [102]. In addition, curcumin derivate, J147, has been shown to upregulate nervous system development functions in diabetic mice. Moreover, functions related with neuron growth, such as proliferation, axon growth and long-term potentiation are the

most significantly changed [103]. Luteolin also shows neuroprotective activity by increasing the levels of brain-derived neurotrophic factor, the action of synapsin I and postsynaptic density protein 95 in the cortex and hippocampus from mice on high fat diet [119]. Likewise, resveratrol has also been widely assessed and chronic treatment improves neuronal injury, not only through attenuation of oxidative stress and neuroinflammation, but also by reducing synaptic loss and increasing synaptic plasticity markers SYN and GAP-43 [150], as well as by inhibiting hippocampal apoptosis through the Bcl-2, Bax and caspase-3 signaling pathways in STZ-induced diabetic rats [151]. Gallic acid may inhibit hippocampal neurodegeneration in diabetic mice not only through its potent antioxidant and anti-inflammatory activities, but also due to its anti-apoptotic properties [118].

Other mechanisms of action have been presented for different compounds and extracts, many of which have focused on the hippocampus, a key area in learning and memory. In this sense *Astragalus Polysacharin* extract may upregulate phosphorylation levels of N-methyl-ᴅ-aspartate receptor, calcium/calmodulin-dependent protein kinase II and cAMP response element-binding protein, as well as reduce the number of dead cells in the CA1 region of the hippocampus from STZ-treated diabetic rats [152]. On the other hand, antioxidants present in bilberry fruits, rich in anthocyanins, influence the morphology of and possibly exhibit beneficial and neuroprotective effects on hippocampal neurons during diabetes [153]. *Pouteria ramiflora* extract administration to STZ-treated rats exerts hippocampal neuroprotection by restoring myosin-Va expression and the nuclear diameters of pyramidal neurons of the CA3 and the polymorphic cells of the hilus [154]. In a T1D rat model, *Garcinia kola* seeds limit neuronal loss in regions involved in cognitive and motor functions, including the motor cortex, the medial septal nucleus an cerebellar Purkinje /granular cell layers [155]. *Urtica dioica* leaves extract also seems to exert it neuroprotective activities by modulating different pathways. It downregulates iNOS, while it upregulates BDNF, TrKB, cyclin D1, Bcl2, autophagy5 and autophagy7 mRNA expression and reduces TNF-α expression in diffrent hippocampal regions. In addition, an overall reduction of neuronal damage and DNA fragmentacion has been observed in the hippocampus from diabetic mice [156]. Other studies have also shown that *Urtica dioica* extract may limit granule cell loss of the dentate gyrus from young diabetic rats. While the positive effect is not observed when the extract is used preventively, it seems to ameliorate hippocampus cell loss when used as a treatment [157]. Similar outcomes have been observed after ginger extract administration, in combination with insulin, to male diabetic rats, showing changes in the expression of cyclin D1 gene and reducing apoptosis in hippocamapal cells [158]. Apart from its well established antioxidant activity, grape seed extract reduces caspases 3 and 9 expression in the hippocampus, ameliorating apoptosis in diabetic rats [113]. Another way of maintaining hippocampus integrity has been observed with an aqueous extract of *Anemarrhena rhizome*, capable of increasing cell proliferation and neurpeptide Y expression in the dentate gyrus from diabetic rats [159]. Lingonberry extract also exerts neuroprotective activity in diabetic rats by reducing oxidative stress, but also by restoring the density of purinergic receptors in the cortex [160]. In addition, in T2D mice with cerebral ischemic injury, chronic treatment with a water-soluble extract from the culture medium of *Ganoderma lucidum* mycelia reduced neuronal cell death and vacuolation in the ischemic penumbra, with reduced number of TUNEL, cleaved caspase-3 cells and the expression of receptor-interaging protein kinase 3 mRNA and protein, confering resistance to apoptosis and necroptosis [161] (Tables 1 and 2, and Figure 1).

2.4. Natural Compounds and Cognitive Impairment in DM

2.4.1. Cognitive Dysfunction Associated with Diabetes

Substantial epidemiological evidence supports that cognitive dysfunction is a common complication of diabetes [162–164]. It has been estimated that 20–70% of patients with DM show cognitive decline, and 60% present at higher risk of dementia [11,12]. Following this idea, it is noteworthy that even prediabetic adults shown accelerated cognitive decline, associated with smaller total brain tissue volume [131]. Different stages of cognitive dysfunction have been associated with diabetes, depending on affected

cognitive features, age or prognosis, andprobably with different underlying mechanisms [165–167]. Previous studies in patients have reported a wide range of diabetes-associated cognitive decrements ranging from subtle changes in cognitive function (that might give rise to cognitive complaints, but should not affect activities of daily life) and mild cognitive impairment, to severe forms like dementia [162,168]. Several factors, including vascular injury, insulin resistance, inflammation and depression, are potential risk factors for cognitive dysfunction in diabetic patients [168–170]. These data are also supported by studies in animal models, where severe cognitive impairment is observed in diabetic animal models that are also dependent on the model under study, the age and evolution of the disease [70,171].

2.4.2. Effect of Natural Compounds and Extracts on Cognitive Impairment Associated with DM

As previously discussed, the mechanisms of action of natural compounds and extracts remain largely elusive, and it is feasible that a combination of different positive effects, including antioxidant, anti-inflammatory, vascular protection, antiapoptotic or proregenerative activities are responsible for observed beneficial effects in DM associated cognitive alterations. Concretely, mangiferin has been shown to counterbalance learning and memory impairments in diabetic rats, treated with STZ, when assessed in the Morris water maze [172]. Similarly, db/db mice on long-term *Mangifera indica* extract, with a high content of mangiferin, significantly improve their performance in the Morris water maze [18]. Moreover, episodic memory alterations are also ameliorated in a very demanding version of the new object discrimination test, and "what", "where" and "when" paradigms are significantly improved [18]. Quercetin also ameliorates STZ-induced spatial learning and memory impairment in the Morris water maze [173,174], reducing the time spent in target quadrant in the test trial and increasing escape latendcy in the elevated plus maze. Similar results have been reported when chrysin [108] or *Andrographis paniculata* extract [175] are administered to STZ-treated rats. Similar outcomes have been reported when *Hedera nepalensis* extract is administered to STZ-aluminium trichloride rat model [176]. Likewise, grape seed proanthocyanidin extract [177], kola nut extract [178] or *Garcinia kola* seeds [155] also improve cognitive impairment in diabetic rat models. *Andrographis paniculata* extract, enriched in andrographolide, improves cognitive function in STZ-treated rats and the effect seems to be mediated by reducing oxidative stress and acetylcholinesterase activity [175]. Similar underlying mechanisms have been described for *Clitorea ternatea* leaves extract, which also improve spatial working memory, spatial reference memory, and spatial working-reference in the Y maze, the Morris water maze and radial arm maze, respectively, in diabetic rats [112]. In addition, studies with *Brassica juncea* extract [179] or resveratrol [150] have reported positive effects on learning and memory in diabetic rats. Equally, hydroalcoholic extract of *Teucrium polium* also limits cognitive impairment in the passive avoidance test while reducing oxidative stress markers in diabetic rats [180]. In addition, cognitive impairment is ameliorated in mice models after administration of *Rosa canina* hydro-alcoholic extract [181] or *Ludwigia octovalvis* extract [182]. Other studies on diabetic mice have shown that *Flos puerariae* extract also improves cognitive impairment after STZ administration, by reducing oxidative stress and restoring cholinergic activity (enhancing cholinacetyltransferase and alleviating acetylcholinesterase activities) in the the cortex from STZ-treated mice [183], and similar outcomes have been reported with *Withania somnifera* and *Aloe vera* extracts [184]. *Bacopa monnieri* [185] and *Urtica dioica* [115,186] extracts restore memory deficits in different diabetic mouse models. Additionally, cognitive impairment in early metabolic alterations, such as prediabetic mice on a high fat diet, improve in the Morris water maze and the step-through task after luteolin [119] or *Ludwigia octovalvis* extract administration [182] (Tables 1 and 2, and Figure 1).

Conclusions: Altogether, natural components and extracts show antioxidant and anti-inflammatory activities at central level, as well as a relevant capacity to reduce vascular damage, contributing altogether to limit neurodegeneration and cognitive derived alterations. Therefore, while the ultimate underlying mechanisms remain largely unknown, they could contribute to expand therapeutic options to treat or reduce central complications associated with DM.

Table 1. Natural compounds and extracts with activity at central level associated with metabolic disorders.

Natural Compound	Action	Plant Source	References
Berberine	Regulation of glucose and lipid metabolism. Reduction of diabetes induced ectopic expression of miR-133a involved in endothelial dysfunction associated with DM. Inhibition of acetylcholine-induced vasorelaxation in the middle cerebral artery → better blood supply to the brain in STZ-treated rats. Reduction of oxidative stress and astrogliosis in the hippocampus from diabetic rats.	*Coptis chinensis* French and others.	[72,73,126]
Patchouli alcohol	Reduction of ischemia/reperfusion damage after middle cerebral artery occlusion in ob/ob mice by limiting infarct volume, protecting blood brain barrier function and decreasing inflammatory markers.	Pogostemonisherba	[74]
Resveratrol	Improvement of neurovascular coupling capacity in T2D patients. Reduction of blood brain barrier permeability and VEGF expression in the hippocampus of diabetic rats. Restriction of astrocytic activation as well as TNF-α, IL-6 transcripts the hippocampus of diabetic rats. Normalization of malonedialdehyde and oxidezed glutathione levels in diabetic rats and strengthening of the action of antioxidants enzymes SOD and catalase. Improvement of neuronal injury by attenuation of oxidative stress and neuroinflammation, and by reducing synaptic loss and increasing synaptic plasticity markers SYN and GAP-43, as well as by inhibiting hippocampal apoptosis through the Bcl-2, Bax and caspase-3 signaling pathways in STZ-induced diabetic rats. Protection against learning and memory alterations in diabetic rats.	*Polygonum cuspidatum*, *Paeonia lactiflora* and *Vitis amurensis*, among others	[75–77,104,150,151]
Quercetin	Enhancement glyoxalase pathway activity, inhibition of AGEs formation and reduction of oxidative stress. Increase of SOD and catalase activities, restoring blood levels of vitamin C and E and ameliorating diabetes-induced oxidative stress. Protection of neuronal PC12 cells against high-glucose-induced oxidative stress, inflammation and apoptosis. Improvement in learning and spatial memory in the Morris water maze.	*Rosa canina*, *Opuntia ficusindica* and *Allium cepa*	[38,75,97–99,173,174]
Mangiferin	Improvement of the function of glyoxalase-1 through activationNrf2/ARE pathway in neurons exposed to chronic high glucose. Protections against learning and memory impairments in diabetic rats, treated with STZ.	*Mangifera indica* Lin, *Rhizoma Anemarrhenae* and *Rhizoma Belamcandae* among others	[100,101,172]
Curcumin	Neuroprotective effects in diabetic rats reducing blood glucose, oxidative stress markers and astrocyte activation in hippocampus. Protection against structural alterations of the hippocampus associated with diabetes.	*Curcuma longa*	[75,102]

Table 1. *Cont.*

Natural Compound	Action	Plant Source	References
J147 curcumin derivative	Increase of curcumin bioavailability and blood brain barrier permeability. Reduction of inflammation by decreasing TNF-α pathway activation and several other markers of neuroinflammation in mice treated with STZ. Upregulation of nervous system development functions in diabetic mice including functions related with neuron growth, proliferation, axon growth and long-term potentiation.	*Curcumin derivate*	[103]
Chrysin	Amelioration of oxidative stress by reducing catalase levels, SOD, and glutathione in the cerebral cortex and hippocampus from diabetic rats. Improvement in spatial memory and learning abilities in Morris water maze test.	*Oroxylum indicum, Passiflora caerulea, Passiflora incarnata, Teloxys graveolens* and *Artocarpus heterophyllus*	[108]
Teasaponin	Reduction of proinflammatory citokines and inflammatory signaling in the hypothalamus from mice on high fat diet.	*Camellia sinensis*	[111]
Gallic acid	Inhibition of hippocampal neurodegeneration via its potent antioxidant and anti-inflammatory effects in diabetic rats as well as its anti-apoptotic properties.	*Phaleria macrocarpa, Peltiphyllum peltatum,* and *Pistacia lentiscus*	[118]
Luteolin	Neuroinflammation amelioration by reducingplasma and brain cytokines levels in a prediabetic mice. Antioxidant and anti-inflammatory effects in diabetic mice. Neuroprotection by increasing the levels of brain-derived neurotrophic factor, the action of synapsin I and postsynaptic density protein 95 in the cortex and hippocampus from mice on high fat diet. Protection against cognitive impairment in early metabolic alterations, such as prediabetic mice on a high fat diet, improvements in the Morris water maze and the step-through task.	*Salvia officinalis, Artemisa annua,* and others	[119,120]
Morin	Inhibition of oxidative stress and inflammation in the brain of STZ-induced diabetic rats. Neuroprotection via attenuation of ROS induced oxidative damage and neuroinflammation in experimental diabetic neuropathy.	*Maclura pomifera* and *Maclura tinctoria*	[123,124]
Rutin	Antioxidant properties in the diabetic rat retina.	*Urtica dioica* and others	[125]

Table 2. Natural extracts with activity at central level associated with metabolic disorders.

Natural Extract	Action	References
Mangifera indica Lin. extract	Reduction of spontaneous central bleeding db/db mice Restriction of microglia activation and associated inflammation in db/db mice after long-term treatment. Limitation of brain atrophy and reduction of tau hyperphosphorylation in db/db mice. Protections against learning and memory impairments in db/db mice in the Morris water maze and new object discrimination tests.	[18]
Ficus deltoidea leaf extract	Increased SOD and glutathione peroxidase values and reduction of thiobarbituric acid reactive substances.	[105]
Scoparia dulcis extract	Increase of plasma SOD, catalase or glutahione peroxidase or glutathione-S-transferase activities and reduction of gluthathione in the brain from STZ diabetic male rats. Reduction of thiobarbituric acid reactive substances and hydroperoxides formation in the brain from diabetic rats	[107]
Gingko biloba extract EGb 761	Scavenging reactive nitrogen and oxygen species, as well as peroxyl radicals.	[35,96,109]
Green tea extracts	Scavenging reactive nitrogen and oxygen species, as well as peroxyl radicals.	[35,110]
Clitorea ternatea leaf extract	Protection against oxidative stress increasing SOD, total nitric oxide, catalase and glutathione levels in the brain of diabetic rats. Improvement of spatial working memory, spatial reference memory, and spatial working-reference memory in the Y maze, the Morris water maze and radial arm maze in diabetic rats.	[112]
Grape seed extract	Beneficial effects on oxidative stress in the hippocampus of STZ-induced diabetes rats. Reduction in expression of inflammatory TNF-α, and NF-κB genes and modulation of AGEs/RAGE/NF-kappaB inflammatory pathway in the brain. Reduction of caspases 3 and 9 expression in the hippocampus, ameliorating apoptosis in diabetic rats. Improvement of cognitive impairment in diabetic rat models.	[113,114,177]
Urtica dioica leaves extract	Antioxidant and anti-inflamatory activities in hippocampus from STZ-induced diabetes in mice. Reduction in the number of astrocytes in the hippocampus from diabetic rats. Protection against memory deficits in different diabetic mouse models. Neuroprotective activities by iNOS downregulation, while it upregulates BDNF, TrKB, cyclin D1, Bcl2, autophagy5 and autophagy7 mRNA expression and reduces TNF-α expression in the hippocampus. Reduction of neuronal damage and DNA fragmentation. Limitation of granule cell loss of the dentate gyrus from young diabetic rats.	[115–117,156,157,186]
Withania somnifera leaf powder	Reduction of gliosis and microgliosis as well as expression of inflammation markers such as PPARγ, iNOS, MCP-1, TNF-α, IL-1β, and IL-6. Improvement of cognitive impairment STZ-treated mice, by reducing oxidative stress.	[121,184]
Extract of *Eryngium carlinae* inflorescences	Reduction of glucose levels by reducing lipid peroxidation, protein carbonylation and reactive oxigen species production, while increasing catalase activity in the brain of diabetic rats.	[122]
Centella asiatica extract	Protection of diabetes tissues from stress via antioxidant and anti-inflammatory mechanisms by brain reduced levels of malondialdehyde, TNF-α, IFN-γ, IL-4 or IL10.	[127]
Ixeris gracilis extract	Antidiabetic, antioxidant, and TNF-α lowering properties in alloxan-induced diabetic mice.	[128]

Table 2. *Cont.*

Natural Extract	Action	References
Malvastrum tricuspidatum extract	Restoration oxidative damage of mitochondrial status in STZ-induced diabetes.	[129]
Astragalus Polysacharin extract	Upregulation of phosphorylation levels of N-methyl-D-aspartate receptor, calcium/calmodulin-dependent protein kinase II and cAMP response element-binding protein, as well as reduction of the number of dead cells in the CA1 region of the hippocampus from STZ-treated diabetic rats.	[152]
Pouteria ramiflora extract	Hippocampal neuroprotection by restoring myosin-Va expression and the nuclear diameters of pyramidal neurons of the CA3 and the polymorphic cells of the hilus in STZ-treated rats.	[154]
Garcinia kola seeds	Reduced neuronal loss in regions involved in cognitive and motor functions, including the motor cortex, the medial septal nucleus a cerebellar Purkinje /granular cell layers in a T1D rat model. Improvement of cognitive abilities in diabetic rat models	[155]
Anemarrhena rhizome aqueous extract	Maintenance of hippocampus integrity by increasing cell proliferation and neurpeptide Y expression in the dentate gyrus from diabetic rats.	[159]
Lingonberry extract	Neuroprotective activity in diabetic rats by reducing oxidative stress and by restoring the density of purinergic receptors in the cortex.	[160]
Ganoderma lucidum mycelia extract	Increased resistance to apoptosis and necroptosis in T2D mice with cerebral ischemic injury.	[161]
Andrographis paniculata extract	Improvement of cognitive function in STZ-treated rats by reducing oxidative stress and acetylcholinesterase activity.	[175]
Hedera nepalensis extract	Improvement of cognitive abilities in STZ-aluminium trichloride rat model.	[176]
Kola nut extract	Protection against cognitive dysfunction in diabetic rat models.	[178]
Brassica juncea extract	Positive effects on learning and memory in diabetic rats.	[179]
hydroalcoholic extract of *Teucrium polium*	Limitation of cognitive impairment in the passive avoidance test and reduction of oxidative stress markers in diabetic rats.	[180]
Rosa canina hydro-alcoholic extract	Amelioration of cognitive impairment in mouse models after treatment.	[181]
Ludwigia octovalvis extract	Improvement of glycemic control and memory performance in mice fed with high fat diet. Protection against cognitive impairment in diabetic mice.	[182]
Flos Puerariae extract	Improvement of cognitive impairment after STZ administration, by reducing oxidative stress and restoring cholinergic activity (enhancing cholinacetyltransferase and alleviating acetylcholinesterase activities) in the cortex.	[183]
Aloe vera extract	Protection against cognitive impairment after STZ administration in mice, by reducing oxidative stress.	[184]
Bacopa monnieri extracts (CDRI-08)	Enhancement of spatial memory in T1D and T2D mice and reduction of oxidative stress.	[185]

Abbreviations

AGEs	Advanced glycation end products
DM	Diabetes mellitus
SOD	Superoxide dismutase
STZ	Streptozotocin
TNF-α	Tumor necrosis factor α
T1D	Type 1 diabetes
T2D	Type 2 diabetes
WHO	World Health Organization

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